Applicants' traverse is respectfully based on the fact that the nucleic acid sequences described in SEQ ID NOS: 23 and 1 (and the amino acid sequences they encode, SEQ ID NOS: 24 and 2) are all encoded by a common genetic locus. Accordingly, Applicants respectfully submit that Groups I and II (claims 1-3) should have been combined into a single group of highly related sequences that share a common nexus of invention. Claims 1-3 in the present invention read on splice variants of a novel ATP-binding transporter protein. One of skill in the art would, therefore, agree that they share a common utility and, as splice variants, they share substantial structural features.

AMENDMENT

In the claims:

Please amend claim 2 so that the text of the amended claim reads as follows:

A1

2. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO: 24; and

(b) hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 23 or the complement thereof.

RESPONSE

I. Status of the Claims

Claim 2 has been amended. Claims 3 and 4 have been cancelled as being drawn to a non-elected invention. No new claims have been added. Claims 1 and 2 are therefore presently pending in the case. For the convenience of the Examiner and in compliance with 37 C.F.R. § 1.121(c)(1)(ii), a marked-up copy of the original claims is attached hereto as **Exhibit A** and a clean copy of the pending claims is attached hereto as **Exhibit B**.

II. Support for the Amended Claim

Claim 2 has been amended to further clarify the claim, and to recite highly stringent conditions. Amendment of claim 2 finds support throughout the specification as originally filed, with particular support and a definition of highly stringent hybridization being found at page 4, lines 7-14.

As the amendment to claim 2 is fully supported by the specification and claims as originally filed, it does not constitute new matter. Entry therefore is respectfully requested.

III. Oath/Declaration

The oath/declaration was deemed defective because non-initialed and/or non-dated alterations had been made on the oath or declaration. Applicants herewith provide another signed Declaration on which the inventor at issue has properly executed his signature.

IV. Rejection of Claims Under 35 U.S.C. § 101

The Action rejects claims 1 and 2 under 35 U.S.C. § 101, allegedly because the claimed invention lacks support by either a specific and substantial asserted utility or a well established utility. Applicants respectfully traverse.

The Action gives a number of reasons for the alleged lack of utility. The Action states that "Applicants have only disclosed that the polynucleotide and encoded polypeptide of the invention are believed to encode novel human proteins (NHP) which share structural similarity to multi-drug resistance proteins (MDRs)." Applicants believe that it is clear that the present invention is drawn to nucleic acid sequences and the amino acid sequences they encode which define novel human transporter proteins that are well known to play a role in multiple drug resistance. This assertion is supported by the applications title, introduction and background of the invention which refer to transporter proteins.

The legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the

assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

The Action alleges that Applicants have failed to characterize the function and activity of the claimed polypeptide sequences. Applicants respectfully disagree and submit that those skilled in the art would clearly believe that the present invention is a transporter and more specifically an ATP-binding cassette transporter (ABC transporter). The biological role for such a protein was described in the specification in section 2 (at page 1 line 25-27). "Transporter proteins are integral membrane proteins that mediate or facilitate the passage of materials across the lipid bilayer." Another activity is, as described in the specification, multiple drug resistance.

Applicants' assertion that the sequences of the present invention encode a transporter is confirmed by, among others, GENBANK Accession No. AY040219, which describes a sequence annotated by others to be the mRNA of human ABC transporter C11. This annotated nucleic acid sequence has a 99% identify with the nucleic acid sequence of SEQ ID NO: 23 (4145 of a total of 4149 bases present in SEQ ID NO: 23). The same is true of GENBANK Accession No. AF367202, which although identified by a different scientists also describes a sequence annotated by a different group to be human ABC transporter C11. As with AY040219, this annotated nucleic acid sequence has a 99% identify with the nucleic acid sequence of SEQ ID NO: 23 (4141 of a total of 4149 bases present in SEQ ID NO: 23). Both of these sequences were defined by third party scientists, wholly unaffiliated with Applicants, as encoding a human ABC transporter. Given this clear evidence that those skilled in the art have independently assigned an ABC transporter function and activity, which includes the utility specifically described in the specification, multiple drug resistance, there can be no question that Applicants' asserted utility for the described sequences is "credible."

Further evidence that the biological significance, function and therefore utility of ABC transporters is well known to those of skill is presented in Exhibits E, F and G, which represent a few of the many available publications regarding the utility of ABC transporters. Applicants note that all of these articles were published after the filing of US provisional application serial no. 60/163,018, filed November 2, 1999, to which the present application claims priority.

These abstracts clearly indicate that ABC transporters, such as the present invention, have well established "real world" substantial utility. As such, the scientific evidence clearly establishes that Applicants have described an invention whose utility is in full compliance with the provisions of 35

U.S.C. section 101, and the Examiner's rejection should be withdrawn.

Although the above discussion is believed to be dispositive of the utility issue, the Applicants would like to further direct the Examiner's attention to the parts of the specification (Sections 5.0 and 5.1) that describe the use of sequences in a gene chip format to provide a high throughput analysis of the relevant cellular "transcriptome".

Evidence of the "real world" substantial utility of the present invention is provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, two such companies (Agilent was acquired by American Home Products and Rosetta acquired by Merck for over 500 million dollars) were viewed to have such "real world" value that they were acquired by large pharmaceutical companies for significant sums of money. The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. The sequences of the present invention describe a novel gene encoding a transporter and provide a unique identifier of the corresponding gene. Such gene chips clearly have utility, as evidenced by hundreds of issued U.S. Patents, such as U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776. The present nucleotide sequences clearly encode a novel human transporter, as detailed throughout the specification. Therefore, as the present sequences are specific markers of the human genome, and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such gene chips.

The Examiner is further requested to consider that, given the huge expense of the drug discovery process, even negative information has great "real world" practical utility. Knowing that a given gene is not expressed in medically relevant tissue provides an informative finding of great value to industry by allowing for the more efficient deployment of expensive drug discovery resources. Such practical considerations are equally applicable to the scientific community in general, in the time and resources that are not wasted chasing what are essentially scientific dead-ends (from the perspective of medical relevance). Clearly, compositions that enhance the utility of such gene chips, such as the presently

claimed nucleotide sequences, must in themselves be useful. Moreover, the presently described novel transporter provides uniquely specific sequence resources for identifying and quantifying full length transcripts that were encoded by the corresponding human genomic locus. Accordingly, there can be no question that the described sequences provide an exquisitely specific utility for analyzing gene expression.

Yet another example of the utility of the present invention is in expanding the utility of data coming from the human genome project. Persons of skill in the art, as well as thousands of venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. All current therapeutics directly or indirectly interact with biological sequences encoded by the human genome, and virtually all future human therapeutics shall do likewise. Consequently, billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304). The results have been a stunning success, as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, Science *291*:1153). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years).

Although Applicants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (C.C.P.A. 1964); *In re Malachowski*, 189 USPQ 432 (C.C.P.A. 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), as a further example of the utility of the presently claimed polynucleotides, the Examiner is respectfully reminded that only a minor percentage of the genome actually encodes exons that in-turn encode polypeptide sequences. The presently described cDNAs provide biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the described cDNA sequences define which exons are actually spliced together to produce an active transcript (*i.e.*, such sequences are generally required to conclusively identify functional exon splice-junctions). The Applicants submit that one skilled in the art would have clearly understood that the above *substantial and specific* utilities as inherent features of the presently described sequences.

For the many convincing reasons described above, the present invention clearly has specific, substantial, credible and well established utility. Therefore, Applicants submit that the rejection of claims 1 and 2 under 35 U.S.C. § 101 has been overcome and the Examiner is respectfully requested to withdraw the pending rejection of claims 1 and 2 under 35 U.S.C. § 101.

V. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

The Action rejects claims 1 and 2 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the claimed invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully disagree.

Applicants submit that as claims 1 and 2 have been shown to have a specific, substantial, credible and well established utility, as detailed in section IV, above. Applicants therefore respectfully request that the rejection of claims 1 and 2 under 35 U.S.C. § 112, first paragraph, be withdrawn.

The Action also rejects claim 2 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is partially avoided by amendment of claim 2 and respectfully traversed.

As demonstrated extensively in section IV, above, the present invention is supported by a specific, substantial, credible and well-established utility. The function of the protein encoded by the sequences of the present invention is that of a transporter, more specifically a ABC transporter.

In addition, contrary to the Examiner's assertion that the breadth of claim 2 is excessive. Applicants respectfully submit that the breadth of claim 2, as filed, was not excessive and that amendment of claim 2 to read on "highly stringent" conditions has reduced its scope further. Applicants respectfully invite the Examiner's attention to the fact that Claim 2, as amended, reads on an isolated nucleic acid molecule comprising a nucleotide sequence that:(a) encodes the amino acid sequence shown in SEQ ID NO: 24; and (b) hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 23 or the complement thereof. As such claim 2 has two limitations. The isolated nucleic acid must encode the amino acid sequence of SEQ ID NO: 24 and it must hybridize under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 23 or the complement thereof.

Applicants respectfully submit that the breadth of claim 2 is not excessive.

Having demonstrated that the present invention is supported by a specific, substantial, credible and well-established utility; that the function of the protein encoded by the sequences of the present invention is that of a transporter, and that the breadth of claim 2 is not excessive Applicants respectfully request withdrawal of the rejection of claims 1 and 2 under 35 U.S.C. § 112, first paragraph.

VI. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph Written Description

The Action does not state which claims have been rejected under 35 U.S.C. § 112, first paragraph for alleged lack of adequate written description. However, in order to move this application more quickly to issuance, Applicant will assume that the Action is referring to Claims 1 and 2 when it states "Claims and are rejected under 35 U.S.C. § 112, first paragraph..." (Action at page 8, line 6). Applicants' assumption is deemed to be reasonable since there are only two claims outstanding.

Regarding the Action's presumed rejection of claims 1 and 2 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse.

35 U.S.C. § 112, first paragraph, requires that the specification contain a written description of the invention. The Federal Circuit in *Vas-Cath Inc. v. Mahurkar* (19 USPQ2d 1111 (Fed. Cir. 1991); "*Vas-Cath*") held that an "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*." *Vas-Cath*, at 1117, emphasis in original. However, it is important to note that the above finding uses the terms reasonable clarity to those skilled in the art. Further, the Federal Circuit in *In re Gosteli* (10 USPQ2d 1614 (Fed. Cir. 1989); "*Gosteli*") held:

> Although [the applicant] does not have to describe exactly the subject matter claimed, ... the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.

Gosteli at 1618, emphasis added. Additionally, *Utter v. Hiraga* (6 USPQ2d 1709 (Fed. Cir. 1988); "*Utter*"), held "(a) specification may, within the meaning of 35 U.S.C. § 112 ¶1, contain a written

description of a broadly claimed invention without describing all species that claim encompasses" (*Utter*, at 1714). Therefore, all Applicants must do to comply with 35 U.S.C. § 112, first paragraph, is to convey the invention with reasonable clarity to the skilled artisan.

Further, the Federal Circuit has held that an adequate description of a chemical genus "requires a precise definition, such as by structure, formula, chemical name or physical properties" sufficient to distinguish the genus from other materials. *Fiers v. Sugano*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993; "*Fiers*"). *Fiers* goes on to hold that the "application satisfies the written description requirement since it sets forth the . . . nucleotide sequence" (*Fiers* at 1607). In other words, provision of a structure and formula - the nucleotide sequence - renders the application in compliance with 35 U.S.C. § 112, first paragraph.

More recently, the standard for complying with the written description requirement in claims involving chemical materials has been explicitly set forth by the Federal Circuit:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. *Univ. of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Thus, a claim describing a genus of nucleic acids by structure, formula, chemical name or physical properties sufficient to allow one of ordinary skill in the art to distinguish the genus from other materials meets the written description requirement of 35 U.S.C. § 112, first paragraph. As further elaborated by the Federal Circuit in *Univ. of California v. Eli Lilly and Co.*:

> In claims to genetic material ... a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA', without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art cannot, as one can do with a fully described genus, visualize or recognize the identity of members of the genus. (Emphasis added)

Thus, as opposed to the situation set forth in *Univ. of California v. Eli Lilly and Co.* and *Fiers*, the nucleic acid sequences of the present invention are not distinguished on the basis of function, or a method of isolation, but in fact are distinguished by structural features - a chemical formula, *i.e.*, the *sequence itself.*

Using the nucleic acid sequences of the present invention (as set forth in the Sequence Listing), the skilled artisan would readily be able to distinguish the claimed nucleic acids from other materials on the basis of the specific structural description provided. Polynucleotides comprising the nucleotide sequence of SEQ ID NO:23, or a nucleotide sequence that encodes SEQ ID NO:24, are within the genus of the instant claims, while those that lack this structural feature lie outside the genus. Claims 1 and 2 thus meet the written description requirement.

Additionally, the Action presumptively rejects claim 2,for lack of written description, arising from the issue that nucleic acid molecules which "hybridize" to those polynucleotides encoding SEQ ID NO: 23, could contain one or more nucleic acid substitutions, deletions, insertions and or additions (Action at page 8,line 9). Applicants respectfully traverse.

Applicants respectfully invite the Examiner's attention to the fact that claim 2, as amended, reads on an isolated nucleic acid molecule comprising a nucleotide sequence that:(a) encodes the amino acid sequence shown in SEQ ID NO: 24; and (b) hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 23 or the complement thereof. As such claim 2 has two limitations. The isolated nucleic acid must encode the amino acid sequence of SEQ ID NO: 24 and it must hybridize under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 23 or the complement thereof.

Therefore, any such "genus" would be very limited. Any isolated nucleic acid that met both of these limitations would have to include "silent" nucleic acid substitutions, most likely in the third or wobble position, such that the new nucleic acid sequence would still encode the amino acid sequence of SEQ ID NO: 24. The insertion of deletion of one or two nucleic acids would be expected to result in a frameshift and the resultant amino acid sequence would be most likely be very different from that of the amino acid sequence of SEQ ID NO: 24. The insertion of 3 nucleic acids would be expected to result in an amino acid sequence that would differ from SEQ ID NO: 24 by one amino acid. Written description for silent substitutions appears in the specification (page 15, lines 5-19). In light of the limitations of amended claim 2, the written description that appears in the specification and what is know to those of skill in the art, amended claim 2 clearly meets the written description requirement.

For each of the foregoing reasons, Applicants submit that the rejection of claims 1 and 2 under 35 U.S.C. § 112, first paragraph, due to lack of written description have been overcome, and respectfully request that the rejection be withdrawn.

VII. Rejection Under 35 U.S.C. § 112, Second Paragraph

The Action rejects claim 2 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the invention. Claim 2 stands rejected because the phrase "stringent conditions" is alleged to be indefinite. Although Applicants believe that this claim as originally filed sufficiently points out and distinctly claims the invention, in order to more rapidly progress the case to allowance, Applicants have amended claim 2 to specify "highly" stringent conditions. Highly stringent conditions for full length molecules are defined in the specification on page 4, lines 7-13. Applicants invite the Examiners attention to the fact that, in addition to the example given, highly stringent conditions are well know in the art and are described at length in Current Protocols in Molecular Biology (Green Publishing Associates, Inc., and John Wiley & Sons, Inc., NY) which is incorporated by reference into the specification of the present invention. Applicants, therefore, respectfully submit that this rejection has been avoided by Applicant's amendment of claim 2 to specify "highly" stringent conditions. Accordingly, the Examiner is respectfully requested to withdraw the pending rejection of claim 2 under 35 U.S.C. § 112, second paragraph.

VIII. Rejection Under 35 U.S.C. § 102(b)

The Action rejects claim 1 under 35 U.S.C. § 102(b), as being allegedly anticipated by Suzuki, *et al.*, (BBRC 238:790-794, 1997).

This rejection is in part directed at a limitation that does not appear in the claim (hybridizes) and therefore cannot properly anticipate claim 1. Withdrawal of the rejection of claim 1 under 35 U.S.C. § 102(b)is therefore respectfully requested.

The Action also states that "Suzuki, *et al.* teach a nucleic acid molecule which has numerous regions of contiguous bases which are 100% identical to SEQ ID NO 23. These regions comprise anywhere from 9 to up to 14 contiguous bases." Suzuki, *et al.* is said to anticipate claim 1, however, claim 1 reads on an isolated nucleic acid comprising at least 24 contiguous bases of nucleotide sequence first disclosed in the NHP gene described in SEQ ID NO 23. As claim 1 reads on at least 24 contiguous bases, it can not be properly anticipated by a sequence containing only 9-14 contiguous bases.